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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,879	11/20/2000	Tatsuya Tamura	TAMURA-5	4195

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EXAMINER
FONDA, KATHLEEN KAHLER

ART UNIT	PAPER NUMBER
1623	9

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,879	TAMURA ET AL.	
	Examiner	Art Unit	
	Kathleen Kahler Fonda, Ph.D.	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-14 and 17-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-14 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection made in a prior Office action and not expressly repeated herein is withdrawn in view of Applicant's arguments and/or amendments.

Applicant is advised that should claim 12 be found allowable, claims 13 and 14 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two or more claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In this case, pharmaceutical composition claims 13 and 14 differ from pharmaceutical composition claim 12 only in a statement of intended use. Thus the claims are duplicative.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 9 lacks positive antecedent basis for "the

matrix metalloprotease inhibitor" and is therefore indefinite. This rejection could be overcome by changing the dependency of claim 9 from claim 1 to claim 3.

Applicant's arguments filed 05-14-03 with respect to the art-based rejections of the claims have been fully considered and are persuasive. The reference as applied in the previous Office action do not teach or suggest conjugates wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer. Therefore, the art-based rejections made in the previous Office action have been withdrawn. However, upon further consideration, new grounds of rejection are made as follows.

Claims 1, 8, 11-14, 19, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by SAKURAI *et al.* (U1). SAKURAI teaches a conjugate of sodium hyaluronate and superoxide dismutase in which the two moieties are covalently linked via a spacer as recited in claim 8. SAKURAI also teaches a method of making such a conjugate by reacting sodium hyaluronate with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, and then reacting the obtained product with superoxide dismutase at a site on the superoxide dismutase that does not interfere with activity. See

the abstract and "Conjugation of SOD with sodium hyaluronate" on page 724. SAKURAI also teaches that the esters described therein may be formulated for administration to mice and rats, for example for treatment of adjuvant arthritis; see the Results, especially the paragraph bridging the columns on page 726. Thus the claims are anticipated.

Claims 1, 3, 5-10, 12-14, 17, 18, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over SAKURAI *et al.* (U1) in view of GALLARDY *et al.* (AB), further in view of FALK *et al.* (C).

Applicant claims a method for treating a patient having joint disease by administering a pharmaceutical composition containing an effective amount of a conjugate comprising at least one therapeutic agent for joint disease and hyaluronic acid or a derivative or salt of hyaluronic acid, wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer. The therapeutic agent may be a matrix metalloprotease inhibitor. The matrix metalloprotease inhibitor may be present in specified concentration and may comprise a specified hydroxamic acid residue.

SAKURAI teaches as set forth above. SAKURAI does not state that conjugates of hyaluronic acid and matrix metalloprotease

inhibitors should be administered to a patient having joint disease.

GALLARDY teaches that hydroxamic acid-based matrix metalloprotease inhibitors may be used to treat diseases "known to be mediated by excess or undesired matrix-destroying metalloprotease activity," such as rheumatoid arthritis; see the abstract and page 10, lines 7-14. The inhibitors of instant claims 7, 9, 20, and 21 are within the scope of the inhibitor designated as formula (1) in the abstract of GALLARDY. GALLARDY also teaches that the matrix metalloprotease inhibitors described therein may be conjugated to carriers (page 5, lines 14-18), or formulated with either conventional excipients (page 10, lines 24-27) or agents effecting tissue penetration (page 11, lines 1-6).

FALK teaches that hyaluronic acid is an agent which enhances tissue penetration of drugs. See column 7, lines 21-32, which teach "compositions . . . comprising an effective non-toxic dosage amount of a drug . . . for example an NSAID and an effective non-toxic dosage amount of a form of hyaluronic acid (preferable hyaluronic acid or a salt thereof) *for the transport of the drug to the site of the pathology and/or trauma*" (emphasis added).

It would have been obvious for a person of ordinary skill in the art at the time of the invention to make a conjugate comprising (a) at least one therapeutic agent for joint disease which is a matrix metalloprotease inhibitor, and (b) hyaluronic acid or a derivative or salt of hyaluronic acid, and to administer it to a patient having joint disease. A worker of ordinary skill in the art would have been motivated to substitute the hydroxamic acid of GALLARDY for the superoxide dismutase of SAKURAI because hydroxamic acid was known to have chemically appropriate binding sites, and both hydroxamic acid and superoxide dismutase were taught to have properties usable for the purpose of treating joint diseases. Treating a patient as recited in claim 22 would have been obvious because SAKURAI had stated that the conditions afflicting the mice and rats treated therein were models for human disease; see the abstract.

Additional motivation is provided by the teaching of GALLARDY that the hydroxamic acids taught therein could be conjugated with carriers including those which effect tissue penetration, coupled with the disclosure of FALK that hyaluronic acid is known to be such a carrier. The invention as claimed would have been obvious because GALLARDY suggested conjugation of hydroxamic acids with a carrier exemplified by hyaluronic acid.

The Examiner additionally notes that Applicant admits at page 7, lines 7-12, that matrix metalloprotease inhibitors maintain their activity even when covalently bound to agarose, which is a polysaccharide similar to hyaluronic acid. Thus there would have been a reasonable expectation of success.

Claims 1, 12-14, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over SAKURAI *et al.* (U1) in view of BEMIS *et al.* (B), further in view of FALK *et al.* (C).

Applicant claims a method for treating a patient having joint disease by administering a pharmaceutical composition containing an effective amount of a conjugate comprising at least one therapeutic agent for joint disease and hyaluronic acid or a derivative or salt of hyaluronic acid, wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer. The therapeutic agent may be a cyclooxygenase-2 inhibitor.

Each of SAKURAI and FALK teaches as set forth above.

BEMIS teaches that cyclooxygenase-2 (COX-2) inhibitors may be used for treatment of joint disease including rheumatoid arthritis and osteoarthritis; see column 21, lines 47-57 as well as column 2, line 6 to column 3, line 20.

It would have been obvious for a person of ordinary skill in the art at the time of the invention to make a conjugate comprising (a) at least one therapeutic agent for joint disease which is a cyclooxygenase-2 inhibitor, and (b) hyaluronic acid or a derivative or salt of hyaluronic acid, wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer, and to administer it to a patient having joint disease. A worker of ordinary skill in the art would have been motivated to substitute the cyclooxygenase-2 inhibitor of BEMIS for the superoxide dismutase of SAKURAI because those skilled in the art at the time of the invention would have recognized that the cyclooxygenase-2 inhibitor had an appropriate site for binding to hyaluronic acid, and both cyclooxygenase-2 inhibitors and superoxide dismutase were known to have properties usable for the purpose of treating joint diseases. Also, as stated above, Applicant admits at page 7, lines 7-12, that certain therapeutic agents for joints maintain their activity even when covalently bound to agarose, which is a polysaccharide similar to hyaluronic acid. Thus there would have been a reasonable expectation of success. Treating a patient as recited in claim 22 would have been obvious because SAKURAI had stated that the conditions afflicting the mice and

rats treated therein were models for human disease; see the abstract.

Claims 1, 12-14, and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over SAKURAI *et al.* (U1) in view of FALK *et al.* (C), further in view of WUNDERLICH *et al.* (D).

Applicant claims a method for treating a patient having joint disease by administering a pharmaceutical composition containing an effective amount of a conjugate comprising at least one therapeutic agent for joint disease and hyaluronic acid or a derivative or salt of hyaluronic acid, wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer. The therapeutic agent may be an antirheumatic agent.

Each of SAKURAI and FALK teaches as set forth above. FALK additionally discloses that NSAIDs including ibuprofen can be formulated with hyaluronic acid, and that an NSAID/hyaluronic acid formulation can be used to treat joint disease. See column 12, lines 13-41; the table at the bottom of column 32; and the Preliminary Report beginning in column 32.

WUNDERLICH confirms that ibuprofen is known to be an antirheumatic drug; see column 1, lines 33-42.

It would have been obvious for a person of ordinary skill in the art at the time of the invention to make a conjugate comprising (a) at least one therapeutic agent for joint disease which is an antirheumatic drug, and (b) hyaluronic acid or a derivative or salt of hyaluronic acid, wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer, and to administer it to a patient having joint disease. A worker of ordinary skill in the art would have been motivated to substitute the NSAID of FALK for the superoxide dismutase of SAKURAI because those skilled in the art at the time of the invention would have recognized that the NSAID had an appropriate site for binding to hyaluronic acid, and both NSAIDs and superoxide dismutase were known to have properties usable for the purpose of treating joint diseases. Also, as stated above, Applicant admits at page 7, lines 7-12, that certain therapeutic agents for joints maintain their activity even when covalently bound to agarose, which is a polysaccharide similar to hyaluronic acid. Thus there would have been a reasonable expectation of success. Treating a patient as recited in claim 22 would have been obvious because SAKURAI had stated that the conditions afflicting the mice and rats treated therein were models for human disease; see the abstract.

Papers relating to this application may be submitted to Technology Center 1600 by facsimile transmission. The number of the fax machine for official papers in Technology Center 1600 is (703) 308-4556. Any document submitted by facsimile transmission will be considered an official communication unless the cover sheet clearly indicates that it is an informal communication.

INTERNET INFORMATION: Secure and confidential access to patent application status information is now available; see http://www.uspto.gov/ebc/index.html for more information. Also, http://www.uspto.gov/web/offices/ac/comp/fin/clonedefault.htm may be used to pay patent maintenance fees, pay non-filing application fees, and maintain USPTO deposit accounts.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kathleen Kahler Fonda, at telephone number (703) 308-1620. Examiner Fonda can generally be reached Monday through Friday from 7:30 a.m. until 4:00 p.m. If the Examiner cannot be reached, questions may be addressed to Supervisory Patent Examiner James O. Wilson at (703) 308-4624. Any inquiry of a general nature or relating to the status of this application should be

directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Kathleen Kahler Fonda, Ph.D., J.D.
Primary Examiner
Art Unit 1623